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EXAMINER
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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 38

Application Number: 09/030,482

Filing Date: 02/25/1998

Appellant(s): Terry P. Snutch and David L. Baillie

Kate H. Murashige

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 04 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement that neither appellants, appellants legal representative nor assignee are aware of any appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 28-33.

Claims 1-27 have been canceled.

Claim 34 withdrawn from consideration as not directed to the elected invention.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 28-33 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7). Appellant's brief includes a statement that states, " The claims may be considered together" but provides no reasons why the claims do not stand or fall together as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art

No prior art is relied upon by the examiner in the rejection of the claims under appeal.

(10) Grounds for Rejection

Claim Rejection, 35 U.S.C. 112, second paragraph

A. Claims 28-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28 is indefinite for the use of "medium hybridization stringency" conditions. It is not clear which conditions represent medium hybridization stringency. The metes and bounds of the group of sequences that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed including wash conditions. Hybridization conditions of temperature, salt and time all determine the polynucleotides that remain bound to the DNA of Claim 28 (a). Although medium stringency conditions represent a narrow range of conditions which can be contrasted with high stringency

and low stringency, without a specific disclosure of the high stringency and low stringency conditions the metes and bounds of medium stringency conditions cannot be determined. The specification does not specifically disclose medium hybridization stringency conditions, used in instant claims. To determine the metes and bounds of medium stringency hybridization what is required are the specific conditions that form the lower limit of medium stringency hybridization conditions and those conditions that form the upper limit of medium stringency hybridization, none of which are disclosed. Therefore the term medium stringency hybridization represents the range of conditions X-Y, where X is the lower limit and Y is the upper limit. The question is what conditions of temperature , salt concentration and time represent X and those that represent Y, so as to allow the metes and bounds of the claim to be determined.

Claim 28, 32 and 33 are indefinite because it is not clear what nucleotide sequence encodes the "functional T-type" calcium channel α1 subunit, and what function is being claimed, so as to allow the metes and bounds of the claims to be determined. The specification and Applicants Response filed 6/11/01 disclose the "amino acid sequence encoded by SEQ ID NO:18 is not complete", and lacks a small portion of the amino acid sequence which is required to obtain functionality (See Applicants Response filed 6/11/01, paper number 23, page 4, second paragraph). What else in addition to the monomer is required form the "functional tetrameric form". The name α_1 subunit does not sufficiently serve to characterize said polypeptide. The application has disclosed a partial sequences for the polynucleotide of SEQ ID NOs:18. The name $\alpha\text{-}_1$ subunit encompasses the complete sequence of the protein and therefore does not sufficiently serve to characterize said protein. Without knowledge of the structure and function of the claimed subunit the metes and bounds of the claim cannot be determined.

Claims 29-31 are indefinite for depending on a base claim or intermediate claim and fail to resolve the issues raised above.

Claim Rejection under 35 USC § 101

Claims 28-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A "specific utility" is a utility that is specific to the subject matter claimed, as opposed to a "general utility" that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A "well established utility" must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention.

The specification has asserted utilities for the specifically claimed invention of claims 28-33. For example, the specification at page 8 asserts that, "the present invention provides partial sequences for novel mammalian (human and rat sequences identified) calcium channel subunit", and knowledge of the polypeptides encoded by the claimed invention "permits the localization and recovery of the complete sequence from human cells, and the development of cell lines which express the novel channel proteins of the invention. These cells may be used for identifying compounds capable of acting as agonists or antagonists to the calcium channels".

Further stated on page 9, "since defects in the novel calcium channel subunits may be associated with a human genetic disease including, but not limited to; epilepsy, migraine, ataxia, hypertension, arrhythmia, angina, depression, small lung carcinoma. Lambert-Eaton syndrome, characterization of such associations and ultimately diagnosis of associated diseases can be carried out with probes which bind to the wild-type or defective forms of the novel calcium channels".

The asserted utilities are not specific or substantial. Neither the specification nor the art of record disclose any disease states treatable by the claimed polynucleotides or its encoded polypeptide. Similarly, neither the specification nor the art of record disclose any instances where blocking any effects of the claimed polynucleotide or its encoded polypeptide reduces the effect of a disease state. Thus the corresponding asserted utilities are essentially methods of treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use especially when the complete sequence of the claimed invention is not known. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed polynucleotide or its encoded polypeptide, further experimentation is necessary to attribute a utility to the claimed invention. See Brenner v. Manson, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a

hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

The specification discloses the α1 subunit of a human calcium channel protein, encoded by claimed DNA molecule, is incomplete (i.e. partial sequence), page 8, first paragraph, and lacking functionality. Further, the Response filed by appellant 6/11/01 (paper number 23, page 4, second paragraph) verifies the "amino acid sequence encoded by SEQ ID NO:18 is not complete", and lacks a portion of the amino acid sequence which is required to obtain functionality (See paper number 23, page 4, second paragraph). Therefore, by Applicants own admission, the claimed polynucleotide encoding the polypeptide of SEQ ID NO:18, is incomplete. Applicant further admits, page 6, the polypeptide is missing "approximately 400 amino acids". Therefore, even though the missing sequence may turn out to be homologous or similar to the C-terminus of other channel proteins, further experimentation is required to complete the missing sequence and determine functionality. Although the complete α1 subunits of calcium channel, alone, can form functional calcium channels, as stated on page 5, lines 15-18, the fact that their electrophysiological and pharmacological properties can be differently modulated by coexpression with any of the four β subunits argues that effects of calcium channel modulation will vary in the native state depending on the availability of four β subunits. The possibility exists that other sub-units, in addition to the ones known may have to be discovered which are required to confer functionality on the claimed α1 subunit, which is required for its physiological function. The specification nor prior art disclose any ligands, agonists or antagonists that bind or affect the functionality of the claimed DNA encoding the α1 subunit of a

human calcium channel protein. Further the specification, on page 9, discloses, "since defects in the novel calcium channel subunits may be associated with a human genetic disease including, but not limited to; epilepsy, migraine, ataxia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, characterization of such associations and ultimately diagnosis of associated diseases can be carried out with probes which bind to the wild-type or defective forms of the novel calcium channels". The wildtype and defective forms are not disclosed. There is no disclosure of any specific disease states associated with dysfunction of claimed DNA (SEQ ID NO:18) encoding the α1 subunit of a human calcium channel protein or defective forms of said protein or polynucleotide. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides. Also, the specification does not predict whether the claimed polynucleotides would be over expressed or under expressed in a specific, diseased tissue compared to the healthy tissue control. Further, the specification does not predict whether the claimed polynucleotide encodes a polypeptide that increases or decreases ion flux in a specific, diseased tissue compared to the healthy tissue control. For example, if a compound is tested on an assay comprising the claimed polynucleotides and affects expression of the polynucleotide negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would acerbate the disease if administered. Similarly it cannot be determined if agonist or antagonist to the polypeptide encoded by SEQ ID NO:18 is a potential good drug for a disease or would acerbate the disease if administered.

The protein encoded by claimed DNA is incomplete and does not form a functional calcium channel and therefore cannot be used in a functional assay where calcium transport is measured. There are no known agonists for the claimed calcium channel therefore the effect of antagonists cannot be determined. Applicant has not disclosed any antagonists or agonists that bind to the protein encoded by claimed DNA that may be used to treat conditions associated with T-type calcium channels or any specific disease states or dysfunctions treatable with said agonists and antagonists. Without knowledge of the functionality of the claimed invention, it is not clear, how one can make the assumption that an antagonist will treat a specific condition. Dysfunction of a calcium channel may be caused by increased or decreased channel activity, therefore a conclusion that an antagonist will treat a disease state is incorrect, the agonist may be required.

The complex nature of calcium signaling, the diversity of the effects of calcium in signaling mechanisms and the effects of the various calcium channels in signaling mechanisms is dependent on the specific calcium channel. The entry of calcium into cells mediates a wide variety of cellular and physiological responses including excitation-contraction coupling, hormone secretion and gene expression (specification, page 1, lines 13-14). Since all calcium channels are not involved with the same disease state and electrophysiological and pharmacological properties can be differently modulated by the β subunits and the cell environment, the effects of calcium channel modulation will vary with cell type and specific calcium channel protein. Therefore an association between the claimed T-type calcium channel and an associated dysfunction cannot be made based on the specification and prior art. The

specific physiological function of the ion channel encoded by the polynucleotide of SEQ ID NO:18 has not been disclosed.

Pertaining to the use of claimed invention as biological target for screening libraries of compounds as candidate pharmaceuticals. As disclosed above the calcium channels have diverse effects. Applicant has not disclosed any specific disease state involve in dysfunction of claimed invention. The instant application does not disclose the biological role of the polypeptide encoded by the polynucleotide of SEQ ID NO:18 or its significance. These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the claimed polynucleotide. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed polynucleotide. This further characterization, however, is part of the act of invention and until it has been undertaken, appellant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which

requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a polynucleotide encoding a polypeptide of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the claimed polynucleotide was, as of the filing date, useful for diagnosis, prevention and treatment of a disease, or for screening compounds. Until some actual and specific significance can be attributed to the polypeptide encoded by the polynucleotide of SEQ ID NO:18, or the gene comprising said polynucleotide, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

The DNA of the instant invention and the protein encoded thereby are compounds which share some structural similarity to calcium ion channels based on sequence similarity. As disclosed by the specification the family of calcium proteins may have diverse effects, and play roles in the pathogenesis of various diseases, require other subunits for binding of ligands Although the family of ion channel proteins having calcium ion protein like domains may share some common structural motifs, various members of the family may have different sites of

action and different biological effects. In the absence of knowledge of the ligand for claimed invention, or the biological significance of this protein, there is no immediately evident patentable use. To employ the polynucleotide of SEQ ID NO:18 or its encoded polypeptide in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for claimed polynucleotide, then the claimed invention as disclosed, does not meet the requirements of 35 U.S.C. §101 as being useful.

The specification nor claims disclose what is the critical structure of the invention that is required for functionality. Since applicant has admitted that the claimed polynucleotide is incomplete and does not encode a complete polypeptide, lacks functionality, therefore, the functional limitation has not been met. As regards the structural limitation, the hybridization conditions specified do not provide a meaningful structural limitation (see rejection under 35 USC 112, second paragraph, above).

For a utility to be "well-established" it must be specific, substantial and credible. All nucleic acids and genes are in some combination useful in drug screening and toxicology testing. However, the particulars of drug screening and toxicology testing with respect to polynucleotide SEQ ID NO:18 are not disclosed in the instant specification. The toxic substances, agonists, antagonists and the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the polypeptide of SEQ ID NO:18.

Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology or drug screening is only useful in the sense that the information that is gained from the array and is dependent on the pattern derived from the array, and says nothing with regard to individual member tested. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Appellants, individual polynucleotide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to diagnosis of disease, there is no requirement that each and every class of DNA sequences or the proteins they encode have an established correlation with a particular disease. However, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. For example, the presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA or protein and the disease. If a molecule is to be used as a

surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

The polypeptide encoded by the polynucleotide of SEQ ID NO:18 belongs to a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases,

telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the calcium channel proteins is disclosed in the specification, pages 1-4. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening or toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed polynucleotide or its encoded polypeptide, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible "real world" manner based on the diversity of biological activities possessed by the Calcium channel proteins. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The utility must be specific, substantial and credible. Applicants' assertion that the claimed invention has utility in drug screening, testing, drug development and disease diagnosis, do not meet the standards for a specific, substantial, and credible or well-established utility for reasons set forth above.

The specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed polynucleotide increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner.

Pertaining to that a utility may be specified even if it applies to a broad class of inventions. The proposition is not sufficient to establish utility for each member of the class.

Specific utility must be shown or be evident for each member of the class. None of the utilities identified have been demonstrated to be specific to the polynucleotide of SEQ ID NO:18 or its encoded polypeptide. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide of SEQ ID NO:18.

A practical utility of an invention may be derived from belonging to a broad class of inventions i.e. the practical utility can be inferred if each and every member of the broad class possesses a common utility. The specification has failed with respect to the polynuclotide of SEQ ID NO:18, having not described the family or the compounds in enough detail to show, by a preponderance of the evidence, that the polynuclotide of SEQ ID NO:18 belongs to a family that has a common utility. The record shows that the Calcium channel protein family is diverse, and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated polynucleotide has utility.

The question at issue is whether or not the broad general assertion that the claimed nucleic acids might be used for *some* diagnostic application in the absence of a disclosure of *which* diagnostic application would be considered to be an assertion of a specific, substantial, and

credible utility. For reasons set forth above the disclosure satisfies none of the three criteria. *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

However, for reasons set forth above, Applicant has not presented sufficient evidence to support specific utility for the polynucleotide of SEQ ID NO:18. The present rejection under § 101 follows *Brenner v. Manson*, as set forth above. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. As Applicant recognizes, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

It can be argued that partial DNA sequences lack utility and that methods of identifying the full length sequence have utility i.e. identifying variants or polynucleotides comprising the polynucleotide of SEQ ID NO: 18. These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the claimed partial polynucleotide of SEQ ID NO:18. There is no doubt that identifying the full length sequences is a valuable technique. However, the claims are not drawn to the technique. The claims are directed to polynucleotides which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Determining the relationship between the claimed polynucleotide or its full length counterpart and relationship to any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed polynucleotide. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The method of identifying the full length sequence of a partial DNA sequence encoding a protein with no disclosed function also has no immediately apparent or "real world" utility as of the filing date because once the complete DNA sequence encoding said protein is isolated, further experimentation is required to associate functionality to said protein.

Claim Rejection under 35 USC § 112, 1st paragraph

B. Claims 28-33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, Claim 28 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The hybridization language recited in the claim does not constitute a meaningful structural limitation. The polypeptide encoded by the nucleic acid of SEQ ID NO:18 is incomplete, the functionality of which has not been disclosed. the claim does not recite a specific functional limitation. The group of polynucleotides that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed, including wash conditions. Hybridization conditions of temperature, salt and time all determine the polynucleotides that remain bound to the DNA of Claim 28 (a). Therefore the recitation of medium stringency hybridization without the disclosure of the specific medium stringency hybridization conditions does not impose specific structural limitations on the claim. Without a disclosure of the specific medium stringency hybridization conditions and specific functional language the claims encompass an unduly broad number of compounds. Since the polynucleotide of SEQ ID NO:18 encodes a non-functional polypeptide it can not be assayed for functionality. It follows that the polynucleotides isolated by hybridization can also not be assigned a function due to the lack of a functional assay. The disclosure of a partial

polynucleotide sequence (SEQ ID NO:18) encoding a non-functional polypeptide or polypeptide whose functionality is not known, does not support claims which encompass an unduly broad number of compounds, given the lack of guidance regarding what sequences would hybridize specifically to the polynucleotide of claim 28 (a) (sequences unrelated, structurally and functionally, are encompassed by the claim since the hybridization conditions do not provide a specific structural limitation), and not other, related sequences. Applicant has not disclosed how to use the unrelated polynucleotides which are isolated by hybridization or how to compare their functionality to the polypeptide encoded by the polynucleotide of SEQ ID NO:18. Therefore like *Ex Parte Maizel*, claim 28, without disclosure of a specific structural limitation (medium stringency hybridization is unduly broad) and a specific disclosed function, the claim encompasses an unduly broad number of compounds.

In Ex parte Maizel, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The only disclosed compound in both the instant case and in Ex parte Maizel is the, naturally occurring compound, polynucleotide represented by SEQ ID NOs: 18, in instant application. The Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of enablement set forth in the patent application. Even though Appellant in Ex parte Maizel urged that the biologically functional equivalents consisted of proteins having amino acid substitutions wherein the substituted amino acids had similar hydrophobicity and charge characteristics such that the substitutions were "conservative" and did not modify the basic functional equivalents of the protein, the Board found that the specification did not support

such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a disclosed partial polynucleotide sequence does not support claims to nucleic acid hybridizing to same, given the lack of guidance regarding what sequences would hybridize specifically to the nucleotide sequence encoding the amino acid sequence encoded by the polynucleotide of SEQ ID NOs: 18, and not other, related sequences. Further many of the DNA isolated by hybridization will be incapable of hybridizing to the nucleic acid of SEQ ID NO:18 (degenerate sequences) and encode protein whose function is unrelated to the protein encoded by the polynucleotide of SEQ ID NO:18. Applicant has not disclosed how to use the unrelated polynucleotides or those encoding unrelated polypeptides. Further the claims drawn to cells comprising claimed isolated DNA molecules and method for producing protein from said cells are not enabled for these reasons given above. The function of the functional T-type channel is not disclosed. Is the function binding to a beta subunit, some cellular signaling event, a disease state etc.?

The specification discloses the polypeptide is incomplete and lacking functionality. Applicants Response filed 6/11/01 verifies the "amino acid sequence encoded by SEQ ID NO:18 is **not complete**", and **lacks a portion of the amino acid sequence which is required to obtain functionality** (See paper number 23, page 4, second paragraph). Therefore, by Applicants own admission, the claimed polynucleotide of SEQ ID NO:18, is incomplete. Applicant further admits, page 6, the **polypeptide is missing "approximately 400 amino acids"**. Even though the missing sequence may turn out to be homologous or similar to the C-terminus of other channel proteins, further experimentation is required to complete the missing sequence. There is no

disclosure which of the millions of polynucleotides isolated by medium stringency hybridization condition would encode the T-type channel having the function claimed, since function is not specifically disclosed.

C. Claims 28-33 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims are drawn to isolated DNA comprising an expression system encoding a functional T-type, low voltage activated channel α1 subunit wherein said encoding nucleotide sequence comprises.

a) a nucleotide sequence encoding the amino acid sequence encoded by SEQ ID NO:18

b) the complement of a nucleotide sequence that hybridizes under conditions of medium

The claims are further drawn to recombinant host cells containing a) or b) and method to prepare cells which produce a functional T-type, low voltage activated channel α1 subunit by introducing the DNA of a) or b), disclosed above.

The specification discloses claimed polynucleotide (SEQ ID NO:18) is a partial sequence of the α_1 subunit. Further the specification states , "These subunits are believed to represent two new types of α_1 subunits of human voltage-dependent calcium channels which have been

designated as type α_{1I} and type α_{1H}", and further states, "The novel α_1 subunits of the invention were identified by screening the *C. Elegans* genomic DNA sequence data base for sequence homologous to previously identified mammalian calcium channel α_1 subunits (page 9, lines 13-20).

The partial DNA sequence (SEQ ID NO:18) is incomplete and encodes a polypeptide lacking functionality. Appellants response filed 6/11/01 (paper number 23) verifies the "amino acid sequence encoded by SEQ ID NO:18 is not complete", and lacks a portion of the amino acid sequence which is required to obtain functionality (See paper number 23, page 4, second paragraph). Therefore, by Applicants own admission, the claimed polynucleotide (SEQ ID NO:18) is incomplete and encodes a polypeptide lacking functionality. Appellant further admits, (paper number 23, page 6, last paragraph) the polypeptide is missing "approximately 400 amino acids". The specification nor prior art disclose the production of an assay system where the DNA of SEQ ID NO:18 has been used to produce a function assay system where calcium flux is measured. Therefore, even though the missing sequence may turn out to be homologous or similar to the C-terminus of other calcium channel proteins, further experimentation is required to complete the missing sequence.

The applicants were not in possession of a functional protein only a partial polypeptide sequence whose functionality has yet to be discovered. Since the polypeptide is incomplete and non-functional there is no disclosure of the critical feature of the invention that is required for functionality. Therefore, the specification discloses a polynucleotide encoding a partial sequence of a polypeptide who's functionality has yet to be determined but the claims are drawn to a genus

of DNA (full length DNA, partial length DNA, genes, chimeric DNA constructs and variants thereof) encoding "functional T-type, low voltage activated calcium channel α1 subunit", which clearly does not meet the written description requirement of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing. There is clearly no possession of the functional protein encoded by the total reading frame of the complete protein. An adequate written description of a DNA, such as the cDNA of instant application, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606. (page 1404). Applicant provide a partial sequence for a non-functional protein and claim the genus of polynucleotides encoding functional full length proteins. The structure, formula, chemical name, or physical properties of a functional full length protein encompassed by the claims has not been disclosed and therefore an adequate written description of the genus of claimed DNA has not been provided.

Further, as stated in the rejection under 112 first and second paragraphs, see above, the medium stringent hybridization do not provide a meaningful structural limitation to claim a reasonable genus of compounds. The variations in nucleotide sequences defined by hybridization conditions can be used for claiming a reasonable genus that includes a single

disclosed polynucleotide sequence and do not unfairly extend the metes and bounds of the invention if the hybridization conditions are clearly defined so as to allow the metes and bounds of the claim to be determined, coupled with a functional limitation, such is not the case in instant invention. Further, since the claims are drawn to a polynucleotide encoding a functional calcium channel protein the claims are also rejected for encompassing the gene encoding by said polynucleotide. The gene is a DNA molecule comprising an expression system for the production of a functional calcium ion channel $\alpha 1$ subunit.

In addition, there is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by using hybridization techniques. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

The specification further fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically

determined. Therefore, the structure of these elements is not conventional in the art and skilled in the art would therefore not recognize from the disclosure that applicant was in possession of the genus of nucleic acid, including genes, comprising SEQ ID NO: 18 or fragments thereof. Further vectors containing genomic DNA nor cells containing said vectors are disclosed. Further methods of using said genomic DNA are rejected for the reasons given above.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Although the nucleotide of SEQ ID NO:18 may encode a α_1 subunit of calcium channel, the specification nor prior art disclose any polynucleotides that may bind the polynucleotide of SEQ ID NO:18 and encode functional α_1 subunit of calcium channel. Only the polynucleotide consisting of the polynucleotide of SEQ ID NO:18 meets the written description requirement.

(11) Response to Argument

(A) <u>The Translation Shown of SEQ ID NO:18 is Alleged to be a Sufficient, Enabling Written Description of a Functional T-type calcium Ion Channel and thus of a Nucleotide Sequence Encoding It.</u>

Appellants arguments are summarized below:

Appellants indicate it is unclear whether the Examiner disputes the statements made in the specification that the α1 subunit of the T-type channel, displayed alone, provides functional calcium ion channel activity.

Appellants argue that calcium channel activity is exhibited by α1 subunit (major pore forming subunit containing a voltage sensor and binding sites for calcium channel antagonists) taken alone.

Appellants argue that Example 2 (describes assessing calcium ion channel activity) states that the α1 calcium channel cDNA may be transfected alone into cells for performing such assessment.

Appellants argue that sworn testimony providing evidence that disclosure of the nucleotide sequence encoding 85% of the full length α1 subunit demonstrates possession of recombinant materials for production of a functional calcium ion channel.

Appellants argue the description of the essential portion missing 15% of the amino acid sequence (domain IV) is inherent in the description of the 85% set forth in the application.

Appellants provide Exhibit D as a rough illustration of voltage-gated ion channels showing four domains I-IV, six transmembrane segments, S4 region and P loop. Appellants state the 85% of the amino acid sequence set forth in the specification extends past the complete domain III as shown in the figure.

Appellants argue the oath by Dr. Terrance Snutch explains that the explicitly disclosed SEQ ID NO:18 starts at the N-terminus and encodes domains I, II, III and pore region and it is well known that structural domains II, III and IV result from evolutionary duplication of domain I,

therefore, the remaining sequence in structural domain IV will be functional if it is simply a replication of the already disclosed sequence of domain III. Further Exhibit C is used to support Appellants' arguments. Also argued is that the nature of the omitted 15% is simply inherent in the description of the 85% and one with ordinary skill in the art would require no experimentation in order to provide a nucleotide sequence encoding a functional calcium ion channel.

Appellants call attention to US Patent (Exhibit E, F and G) in which patents were issued for incomplete human α2 subunit, non-functional ion channels and claiming high stringency.

For the reasons given above, appellants request that the board recognize that an adequate written description of claimed subject matter has been provided.

Exhibits A and B (Declarations by Dr. Terrance Snutch) have been considered, and are discussed below. As an aside, it is noted that Dr. Terrance Snutch is an Appellant in instant application, and thus is a concerned party.

Exhibits C, D and F will not be admitted because they are submitted after the case has been appealed and there is no showing of good and sufficient reasons why they were not earlier presented.

Exhibits G and H (both US Patents) have been considered because they were presented before the case was appealed, and are discussed below.

Appellants' arguments have been fully considered but not found persuasive for the reasons given below:

The specification page 8, first paragraph, discloses that, "the present invention provides partial sequences for novel mammalian (human and rat sequences identified) calcium channel subunit", and knowledge of the polypeptides encoded by the claimed invention "permits the localization and recovery of the complete sequence from human cells, and the development of cell lines which express the novel channel proteins of the invention". The specification discloses the α1 subunit of a human calcium channel protein, encoded by claimed DNA molecule, is incomplete (i.e. partial sequence), page 8, first paragraph. No disclosure is provided in the specification as to its functionality. Further, the Response filed by appellant 6/11/01 (paper number 23, page 4, second paragraph) specifically states, "Briefly, the amino acid sequence encoded by **SEQ ID NO:18 is not the complete α_1** calcium ion channel; however, the amino acid sequence encoded by **SEQ ID NO:18 contains virtually all of the elements essential for functionality**, and by virtue of the understanding of the structure of α_1 in general, and the nature of the relationship of one portion to another, the deduced amino acid sequence encoded by SEQ ID NO:18 provides the skilled artisan with information to design an amino acid sequence which represents the small portion of the amino acid sequence lacking and required in order to obtain functionality". Therefore the response filed by 6/11/01 (paper number 23, page 4, second paragraph) verifies the amino acid sequence encoded by SEQ ID NO:18 is not complete, and lacks a portion of the amino acid sequence which is required to obtain functionality. Therefore, since all the sequence is not provided, the skilled artisan must design an amino acid sequence which represents the small portion of the amino acid sequence lacking and required in order to obtain functionality. Since the polynucleotide of SEQ ID NO:18 does not contain all, **but**

virtually all of the elements essential for functionality, the missing element must first be identified or synthesized and then incorporated into the polynuclotide of SEQ ID NO:18 to assess a functionality that has not been defined. Therefore, by Appellants own admission, the claimed polynucleotide encoding the polypeptide of SEQ ID NO:18, is incomplete. The full polynucleotide is required to obtain functionality. Applicant further discloses on the record (paper number 23, page 6, last paragraph) the polypeptide is missing "approximately 400 amino acids", and "the missing approximately 400 amino acids sequence is highly homologous to three homologous domains included in the retrieved sequence". Since the "approximately 400 amino acids" are missing it cannot be concluded that the missing fragment is homologous to other parts of the molecule since the claimed invention is a T-type channel, which is activated at lower potential and has not been previously characterized as associated with a particular nucleotide sequence or gene. Therefore, even though the missing sequence may turn out to be homologous or similar to the C-terminus of other channel proteins, further experimentation is required to complete the missing sequence and determine functionality. The complete or partial polypeptide encoded by polynucleotide of SEQ ID NO:18 has not been crystallized, and the specific domain structure not shown in the prior art or the specification. Specific information required to produce a functional T-type channel encoded by the polynuclotide comprising SEQ ID NO:18 is missing. For example at what specific nucleotide do domains I, II, III, and IV start and end? Where does the pore region start and end? Where does the P loop start and end? Which fragments consist of the six transmembrane regions? Further the functional T-type channel encoded by the polynuclotide comprising SEQ ID NO:18 has not been shown to be active in any assay system.

The declaration of Dr. Terrance Snutch does not disclose that the polypeptide encoded by the polynuclotide SEQ ID NO:18 is functional, it states that one of ordinary skill in the art would understand that it encodes about 85% of a functional T-type calcium cannel α1 subunit and would be able to design an amino acid sequence representing the missing C-terminal portion based on homology to the three domains encoded by SEQ ID NO:18 and would be able to construct an expression system containing a nucleotide sequence encoding a functional T-type calcium ion channel α1 subunit without obtaining a full length clone. Dr Snutch has used sequence homology between calcium family members to place instant invention in the general family of L-type channel proteins but states that nucleotide sequence set forth in SEQ ID NO:18 is relatively distantly related to the two branches represented by α1 subunits A, B, E and α1 subunits S, C and D. Channel proteins have different structures, functions and affected differently by mutations, as disclosed in the specification, pages 1-6, therefore prior art and instant application cannot be used to generate a specific fragment of nucleotides that would provide a functional channel protein comprising the polynucleotide of SEQ ID NO:18, since said polynucleotide is the first member of a new class of channel proteins. There is no disclosure in instant specification or prior art that discloses which sequence of nucleotides needs to be added to the polynucleotide of SEQ ID NO:18 to generate a functional protein. Also it must be noted that a single nucleotide change can cause mutations which may cause changes in the tertiary structure which may have drastic effects on the protein structure and function. Therefore without isolating the full length polynucleotide comprising SEQ ID NO:18, from naturally occurring

molecules, generating functional polynucleotide by chemical synthesis would be a trial and error approach.

In addition, there is no description in the specification of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by using hybridization techniques. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Further Applicant draws attention to issued patent 6,358,706 and 6,309,858. Appellants reference to Patent Number 6,358,706 and 6,309,858 as support for arguments under written description for establishing possession of the claimed invention is not persuasive because each application is examined on its own merits. In the decision of *In re Hutchison*, 69 USPQ 138 (CCPA, 1946), the court held that

> "We are not concerned, of course, with the allowed claims in either the patent or in this application. The sole question for our determination is whether the six article claims on appeal were properly rejected below, and this we pass upon without further reference to, and without comparing them with, the claims in the patent or the claims which stand allowed in this application."

In essence, the position in the instant application that each application is examined on its own merits can be found in the judicial precedent cited above. The rejections in the instant application will only be withdrawn if they are shown to be legally or factually unsound.

B. Medium Hybridization Stringency are Alleged to be Sufficiently Definite to Comply with the Statute.

Appellant argues:

Medium hybridization stringency defines a narrow range of sequence homology and refers to paragraph 4 of the Snutch declaration, Exhibit B. Appellant specifically states, "As stated in the Dr. Snutch declaration, it is understood that it is the wash conditions that determine the ultimate stringency of the hybridization; these conditions for medium stringency are known in the art to range from 0.15-0.3% SDS, 2XSSPE and 55°-65°C. These conditions represent a homology of at least 70%" and "would be such that high voltage activated channel-encoding DNA would be excluded". Appellant also asserts that in the present instance, there is a declaration of record, uncontroverted, which sets forth the understanding in the art of specific metes and bound of medium stringency. A statement is made that it should be apparent that there is nothing inherently uncertain or indefinite about claiming a range as opposed to a single value for a parameter.

The US patent 5,710,250 (Exhibit E) contains claims to "high stringency", where "high stringency was nowhere defined in the specification.

For the reasons given above, appellants request that the Board reverses the rejection under 35 U.S.C 112, second paragraph.

Appellants arguments have been fully considered but not found persuasive.

Examiner has reviewed Exhibit B, the Snutch Declaration and cannot find a statement, " it is understood that it is the wash conditions that determine the ultimate stringency of the hybridization; these conditions for medium stringency are known in the art to range from 0.15-0.3% SDS, 2XSSPE and 55°-65°C". The Snutch declaration discloses medium stringency hybridization to colony or plaque lifts on nitrocellulose or nylon membranes is **typically** performed at 62°C to 65°C in the presence of a probe in a solution containing 5 times Denhardt's, 0.3% SDS and 5X SSPE. **Typically** preformed medium stringency hybridization conditions is not a definition of the range of temperature, salt, and time needed to define medium stringency hybridization, as well as wash conditions so as to allow the metes and bounds to be determined. Snutch also discloses medium stringency hybridization may be performed at 42°C in a solution containing 50% formamide, 5 times Denhardt's, 02-0.7% SDS and 5X-6X SSPE or the alternative buffer may be SSC from 5X to 6X. Again the disclosure of medium stringency hybridization **may** be performed at 42°C in a solution containing 50% formamide, 5 times Denhardt's, 02-0.7% SDS and 5X-6X SSPE or the alternative buffer may be SSC from 5X to 6X is not a definition of the range of temperature, salt, and time needed to define medium stringency hybridization, as well as wash conditions so as to allow the metes and bounds to be determined. Snutch also discloses, "After hybridization the hybridization solution is removed and membranes are washed several times in a solution typically containing 0.1% to 0.3%SDS and 2X SSPE to 0.2X SSPE. The temperature of medium stringency washing typically can vary from 55°C to 65°C . The disclosure of washing several times in a solution **typically** containing 0.1% to

0.3%SDS and 2X SSPE to 0.2X SSPE where the temperature of medium stringency washing **typically** can vary from 55°C to 65°C is not a definition of the range of temperature, salt, and time needed to define medium stringency hybridization, as well as wash conditions so as to allow the metes and bounds to be determined. The declaration of Snutch only discloses certain conditions that can be used to perform medium stringency hybridization, but does not provide a definition of said hybridization conditions.

The metes and bounds of the group of polynucleotides that would meet the limitations of the claim depend upon the precise conditions under which hybridizations were performed, including wash conditions. Hybridization conditions of temperature, salt and time all determine the polynucleotides that remain bound to the DNA of Claim 28 (a). Although medium stringency conditions represent a narrow range of conditions which can be contrasted with high stringency and low stringency, without a specific disclosure of the high stringency and low stringency conditions the metes and bounds of medium stringency conditions cannot be determined. The disclosure by Dr. Terry P. Snutch does not overcome the deficiency in the specification which does not specifically disclose medium hybridization stringency conditions, used in instant claims. To determine the metes and bounds of medium stringency hybridization what is required are the specific conditions that form the lower limit of medium stringency hybridization conditions and those conditions that form the upper limit of medium stringency hybridization, none of which are disclosed. Therefore the term medium stringency hybridization represents the range of conditions X-Y, where X is the lower limit and Y is the upper limit. The

question is what conditions of temperature , salt concentration and time represent X and those that represent Y, so as to allow the metes and bounds of the claim to be determined.

Further Appellant argues that it is understood that it is the wash conditions that determine the ultimate stringency of hybridization. This statement may be correct but "medium stringency hybridization" does not encompass washing alone. Apart from the washing step, other conditions involved in the initial hybridization conditions also have an important impact on the molecules ultimately isolated, otherwise why go through the elaborate process of designing and using said conditions. For example, performing hybridization at 0.3% SDS and 0.2X SSPE at 65°C and washing with 0.3%SDS and 2X SSPE at 55°C would isolate a differing pattern of polynuclotides as compared to performing hybridization at 0.3% SDS and 5X SSPE at 42°C and washing with 0.3%SDS and 2X SSPE at 55°C. In the example shown the wash conditions are the same but hybridization conditions vary.

Further, Appellant draws attention to issued patent 5,710,250 (Exhibit E). Appellants reference to Patent Number 5,710,250 as establishing a validity for the use of "medium stringency hybridization" is not persuasive because each application is examined on its own merits. In the decision of *In re Hutchison*, 69 USPQ 138 (CCPA, 1946), the court held that

> "We are not concerned, of course, with the allowed claims in either the patent or in this application. The sole question for our determination is whether the six article claims on appeal were properly rejected below, and this we pass upon without further reference to, and without comparing them with, the claims in the patent or the claims which stand allowed in this application."

In essence, the position in the instant application that each application is examined on its own merits can be found in the judicial precedent cited above. The rejections in the instant application will only be withdrawn if they are shown to be legally or factually unsound.

In conclusion, medium stringency hybridization conditions have not been disclosed in the specification nor any references supplied which disclose the absolute lower and upper limits of said conditions so that the metes and bounds of the claims can be determined.

C. The Utility of the Claimed Subject Matter is Alleged to be Established

Appellant argues:

The recombinant α1 subunits can be used in an assay system to identify compounds which would be useful in treating specifically enumerated diseases including epilepsy, migraine, ataxia, hypertension, schizophrenia, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome.

The utilities in the instant application is described in the same manner as that disclosed in US Patents 6,309,858 and 6,358,706 (Exhibits G and H).

Exhibit C establishes that compounds that are selective for T-type channels would be useful pharmacologically. Exhibit C will not be admitted because it was submitted after the case has been appealed and there is no showing of good and sufficient reasons it was were not earlier presented.

Accordingly, reversal of the rejection grounded in lack of utility is requested. For the reasons given above, appellants request that the Board reverses the rejection under 35 U.S.C 101.

Appellants arguments have been fully considered but not found persuasive.

The asserted utilities are not specific or substantial. Neither the specification nor the art of record disclose any disease states treatable by the claimed polynucleotides or its encoded polypeptide. There are no compounds identified by use of the recombinant α1 subunits of (SEQ ID NO:18), in an assay system, which would be useful in treating specifically enumerated diseases including epilepsy, migraine, ataxia, hypertension, schizophrenia, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome. Similarly, neither the specification nor the art of record disclose any instances where blocking any effects of the claimed polynucleotide or its encoded polypeptide reduces the effect of a disease state. Thus the corresponding asserted utilities are essentially methods of treating a "laundry list" of diseases or conditions, or identifying compounds that may bind to the polypeptide encoded by the polynucleotide of SEQ ID NO:18, but at present have not been shown to treat a specific disease. Said asserted utilities does not define a "real world" context of use. Treating a "laundry list" of diseases or a condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use especially when the claimed polynucleotide is a partial sequence lacking functionality. Similarly identifying compounds by use of claimed polynucleotide for treating a "laundry list" diseases or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use especially when the claimed polynucleotide is a partial sequence lacking functionality. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed polynucleotide or its encoded polypeptide, further experimentation is necessary to attribute a utility to the claimed invention.

See Brenner v. Manson, 383 U.S. 519, 535–36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

The specification discloses the α1 subunit of a human calcium channel protein, encoded by claimed DNA molecule, is incomplete (i.e. partial sequence), and lacking functionality (see rejection under USC 35 101, above). Further, the Response filed by appellant 6/11/01 (paper number 23, page 4, second paragraph) verifies the "amino acid sequence encoded by SEQ ID NO:18 is not complete", and lacks a portion of the amino acid sequence which is required to obtain functionality (See paper number 23, page 4, second paragraph). Therefore, by Applicants own admission, the claimed polynucleotide encoding the polypeptide of SEQ ID NO:18, is incomplete. Appellant further admits, page 6, the polypeptide is missing "approximately 400 amino acids". Therefore, even though the missing sequence may turn out to be homologous or similar to the C-terminus of other channel proteins, further experimentation is required to complete the missing sequence and determine functionality. Although the complete α1 subunits of the calcium channel alone can form functional calcium channels, as stated on page 5, lines 15-18, the fact that their electrophysiological and pharmacological properties can be differently modulated by coexpression with any of the four β subunits argues that effects of calcium channel modulation will vary in the native state depending on the availability of four β subunits. The possibility exists that other subunits, in addition to the ones known may have to be discovered

which are required to confer functionality on the claimed α1 subunit, which is required for its physiological function. The specification nor prior art disclose any ligands, agonists or antagonists that bind or affect the functionality of the claimed DNA encoding the α1 subunit of a human calcium channel protein. There is no disclosure of any specific disease states associated with dysfunction of claimed DNA (SEQ ID NO:18) encoding the α1 subunit of a human calcium channel protein or defective forms of said protein or polynucleotide. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides. Also, the specification does not predict whether the claimed polynucleotides would be over expressed or under expressed in a specific, diseased tissue compared to the healthy tissue control. Further, the specification does not predict whether the claimed polynucleotide encodes a polypeptide that increases or decreases ion flux in a specific, diseased tissue compared to the healthy tissue control. For example, if a compound is tested in an assay comprising the claimed polynucleotide and affects expression of the polynucleotide negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would acerbate the disease if administered. Similarly it cannot be determined if agonist or antagonist to the polypeptide encoded by SEQ ID NO:18 is a potential good drug for a disease or would acerbate the disease if administered. It is not disclosed whether agonists or antagonists identified by use of claimed polynucleotide would be effective at treating epilepsy, migraine, ataxia, hypertension, schizophrenia, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome. Not a single compound has been identified by the use of claimed polynuclotide. The claimed polynucleotide has not even been expressed in a functional assay.

Since the protein encoded by claimed DNA is incomplete and has not been shown to form a functional calcium channel, it therefore cannot be used in a functional assay where calcium transport is measured. There are no known agonists for the claimed calcium channel therefore the effect of antagonists cannot be determined. Applicant has not disclosed any antagonists or agonists that bind to the protein encoded by claimed DNA that may be used to treat conditions associated with T-type calcium channels or any specific disease states or dysfunctions treatable with said agonists and antagonists. Without knowledge of the functionality of the claimed invention, it is not clear, how one can make the assumption that an antagonist or agonists will treat a specific condition. Dysfunction of a calcium channel may be caused by increased or decreased channel activity, therefore a conclusion that an antagonist will treat a disease state is incorrect, the agonist may be required.

The complex nature of calcium signaling, the diversity of the effects of calcium in signaling mechanisms and the effects of the various calcium channels in signaling mechanisms is dependent on the specific calcium channel. The entry of calcium into cells mediates a wide variety of cellular and physiological responses including excitation-contraction coupling, hormone secretion and gene expression (specification, page 1, lines 13-14). Since all calcium channels are not involved with the same disease state and electrophysiological and pharmacological properties can be differently modulated by the β subunits and the cell environment, the effects of calcium channel modulation will vary with cell type and specific calcium channel protein. Therefore an association between the claimed T-type calcium channel and an associated dysfunction cannot be made based on the specification and prior art. The

specific physiological function of the ion channel encoded by the polynucleotide of SEQ ID NO:18 has not been disclosed.

The use of claimed invention as a biological target for screening compounds as candidate pharmaceuticals is discussed below. As disclosed above the calcium channels have diverse effects. Appellant has not provided any data showing a specific disease state involved in dysfunction of claimed invention. The instant application does not disclose the biological role of the polypeptide encoded by the polynucleotide of SEQ ID NO:18 or its significance. These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the claimed polynucleotide. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed polynucleotide. This further characterization, however, is part of the act of invention and until it has been undertaken, appellants claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which

requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a polynucleotide encoding a polypeptide of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the claimed polynucleotide was, as of the filing date, useful for diagnosis, prevention and treatment of an disease, or for screening compounds. Until some actual and specific significance can be attributed to the polypeptide encoded by the polynucleotide of SEQ ID NO:18, or the gene comprising said polynucleotide, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

The DNA of the instant invention and the protein encoded thereby are compounds which share some structural similarity to calcium ion channels based on sequence similarity. As disclosed by the specification the family of calcium proteins may have diverse effects, and play roles in the pathogenesis of various diseases, require other subunits for binding of ligands Although the family of ion channel proteins having calcium ion protein like domains may share some common structural motifs, various members of the family may have different sites of

action and different biological effects. In the absence of knowledge of the ligand for claimed invention, or the biological significance of this protein, there is no immediately evident patentable use. To employ the polynucleotide of SEQ ID NO:18 or its encoded polypeptide in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for claimed polynucleotide, then the claimed invention as disclosed, does not meet the requirements of 35 U.S.C. §101 as being useful.

For a utility to be "well-established" it must be specific, substantial and credible. All nucleic acids and genes are in some combination useful in drug screening. However, the particulars of drug screening with respect to polynuclotide SEQ ID NO:18 are not disclosed in the instant specification. The agonists, antagonists and the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the polypeptide of SEQ ID NO:18. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Even if the expression of Appellants individual polynucleotide is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotide has no "well-established" use. The artisan

is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to diagnosis of disease, there is no requirement that each and every class of DNA sequences or the proteins they encode have an established correlation with a particular disease. However, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. For example, the presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA or protein and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further

research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

The polypeptide encoded by the polynucleotide of SEQ ID NO:18 belongs to a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the calcium channel proteins is disclosed in the specification, pages 1-4. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening or toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to

virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld; therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed polynucleotide or its encoded polypeptide, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible "real world" manner based on the diversity of biological activities possessed by the Calcium channel proteins. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The utility must be specific, substantial and credible. Applicants' assertion that the claimed invention has utility in drug screening, testing, drug development and disease diagnosis, do not meet the standards for a specific, substantial, and credible or well-established utility for reasons set forth above.

The specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed polynucleotide increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner.

Pertaining to that a utility may be specified even if it applies to a broad class of inventions. The proposition is not sufficient to establish utility for each member of the class. Specific utility must be shown or be evident for each member of the class. None of the utilities identified have been demonstrated to be specific to the polynucleotide of SEQ ID NO:18 or its encoded polypeptide. One of ordinary skill in the art must understand how to achieve an immediate and practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide of SEQ ID NO:18.

Pertaining to a practical utility of an invention may be derived from belonging to a broad class of inventions. The requirement in any particular case, however, is that practical utility can be inferred if each and every member of the broad class possesses a common utility. The specification has failed with respect to the polynucleotide of SEQ ID NO:18, having not described the family or the compounds in enough detail to show, by a preponderance of the evidence, that the polynucleotide of SEQ ID NO:18 belongs to a family that has a common

utility. The record shows that the Calcium channel protein family is diverse, and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated polynucleotide has utility.

The question at issue is whether or not the broad general assertion that the claimed nucleic acids might be used for *some* diagnostic application in the absence of a disclosure of *which* diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

However, for reasons set forth above, Applicant has not presented sufficient evidence to support specific utility for the polynucleotide of SEQ ID NO:18. The present rejection under §

101 follows *Brenner v. Manson*, as set forth above. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action.

The claims are not drawn to the technique. The claims are directed to polynucleotides which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Determining the relationship between the claimed polynucleotide or its full length counterpart and relationship to any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed polynucleotide. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The method of identifying compounds using claimed partial length DNA sequence encoding a protein with no disclosed function, has no immediately apparent or "real world" utility as of the filing date because once the complete DNA sequence encoding said protein is isolated, further experimentation is required to associate functionality to said protein.

Exhibits C will not be admitted because it was submitted after the case has been appealed and there is no showing of good and sufficient reasons why it was earlier presented.

Further Applicant draws attention to issued patent 6,358,706 and 6,309,858. Appellants reference to Patent Number 6,358,706 and 6,309,858 as support for arguments for establishing patentable utility for the claimed polynucleotide is not persuasive because each application is examined on its own merits. In the decision of *In re Hutchison*, 69 USPQ 138 (CCPA, 1946), the court held that

> "We are not concerned, of course, with the allowed claims in either the patent or in this application. The sole question for our determination is whether the six article claims on appeal were properly rejected below, and this we pass upon without further reference to, and without comparing them with, the claims in the patent or the claims which stand allowed in this application."

In essence, the position in the instant application that each application is examined on its own merits can be found in the judicial precedent cited above. The rejections in the instant application will only be withdrawn if they are shown to be legally or factually unsound.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

NSB
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